Isis Pharmaceuticals Reports Positive Clinical Data From Lp(a) Lowering Drugs

November 8, 2015

Webcast to review data scheduled for Sunday, November 8 at 1:00 p.m. Eastern Time

CARLSBAD, Calif., and CAMBRIDGE, Mass., Nov. 8, 2015 /PRNewswire/ -- Isis Pharmaceuticals, Inc. (NASDAQ: ISIS), and its subsidiary, Akcea Therapeutics, today announced positive results from a Phase 2 study of ISIS-APO(a)$_{Rx}$ in which patients with high lipoprotein(a), or Lp(a), achieved reductions in Lp(a) of up to 94 percent, with a mean reduction of 71 percent. Lp(a) is a known driver of cardiovascular disease. They also announced results from a Phase 1/2a study of ISIS-APO(a)-L$_{Rx}$ in which subjects with elevated Lp(a) achieved dose-dependent reductions in Lp(a) of up to 99 percent. ISIS-APO(a)-L$_{Rx}$ is a Ligand Conjugated Antisense (LICA) version of ISIS-APO(a)$_{Rx}$. ISIS-APO(a)-L$_{Rx}$ demonstrated a greater than 30-fold increase in potency in humans as compared to ISIS-APO(a)$_{Rx}$. Data from both the Phase 2 and Phase 1/2a studies were presented today at the American Heart Association Scientific Sessions by Joseph Witztum, M.D., distinguished professor of medicine and director of the atherosclerosis research group at the University of California, San Diego.

"Based on strong evidence, it is well accepted that elevated levels of Lp(a) are a key driver of cardiovascular disease. Because Lp(a) levels are largely unchanged throughout a person's lifetime, high Lp(a) levels present at birth can result in cumulative damage, which can be significant throughout the lifetime of a patient. ISIS-APO(a)-L$_{Rx}$ is the only drug in clinical development that can specifically and robustly lower Lp(a) in patients with elevated Lp(a)," said Sotirios Tsimikas, M.D., professor of medicine and director of vascular medicine at the University of California, San Diego, and vice president of clinical development at Isis Pharmaceuticals. "In the studies presented today, patients achieved substantial reductions in Lp(a) that were irrespective of their incoming Lp(a) levels. These data support developing ISIS-APO(a)-L$_{Rx}$ for patients with high Lp(a), especially patients with the highest Lp(a) levels, who are also at the greatest risk."

Significant Reductions of Lp(a) in Phase 2 Study of ISIS-APO(a)$_{Rx}$

In the Phase 2 study, patients with high or very high Lp(a) treated with ISIS-APO(a)$_{Rx}$ achieved substantial reductions in Lp(a) of up to 94 percent with a mean reduction of 71 percent ($p \leq 0.001$). In this study, patients treated with ISIS-APO(a)$_{Rx}$ achieved equal reductions of Lp(a) regardless of incoming Lp(a) levels. The Phase 2 study was a randomized, double-blind, placebo-controlled, dose-titration 12 week study evaluating ISIS-APO(a)$_{Rx}$ in 65 patients with Lp(a) levels that were high (greater than or equal to 50 mg/dL and less than 175 mg/dL) or very high (greater than or equal to 175 mg/dL). In this study, treatment with ISIS-APO(a)$_{Rx}$ was generally well tolerated with no safety issues observed.

Significant, Sustained Lp(a) Reduction in Phase 1/2a Study of ISIS-APO(a)-L$_{Rx}$

In the Phase 1/2a study, subjects who received a single, low volume, subcutaneous injection of 10 mg, 20 mg, 40 mg or 80 mg of ISIS-APO(a)-L$_{Rx}$ achieved robust, dose-dependent and durable reductions of Lp(a). Subjects who received a single dose of 80 mg ISIS-APO(a)-L$_{Rx}$ achieved substantial reductions in Lp(a) of up to 97 percent and a mean reduction of 79 percent ($p \leq 0.01$) at 30 days. The long duration of effect resulted in significant Lp(a) reductions of nearly 50 percent at 90 days after the single dose.

Subjects who received multiple doses of 10 mg, 20 mg or 40 mg of ISIS-APO(a)-L$_{Rx}$ achieved dose-dependent, significant reductions in Lp(a) of up to 99 percent, and a mean reduction of up to 92 percent ($p \leq 0.001$). In this study, subjects treated with ISIS-APO(a)-L$_{Rx}$ achieved similar reductions of Lp(a) regardless of incoming Lp(a) levels. The safety and tolerability profile of ISIS-APO(a)-L$_{Rx}$ to date supports continued development: out of 159 injections there were no injection site reactions or flu-like symptoms reported.

"The enhanced potency of ISIS-APO(a)-L$_{Rx}$, the opportunity for very infrequent dosing and the good safety and tolerability profile significantly expands the patient populations we plan to pursue for this drug. These data and our experience with ISIS-APO(a)$_{Rx}$ support our plans to rapidly move forward with the development of ISIS-APO(a)-L$_{Rx}$ to treat patients with a variety of Lp(a)-driven cardiovascular diseases. We have a robust development program that addresses near, mid and long-term commercial opportunities for ISIS-APO(a)-L$_{Rx}$ by focusing initially on patients who have the greatest need and, in the long-term, on patients with more generalized Lp(a)-driven cardiovascular risk," said Paula Soteropoulos, president and chief executive officer of Akcea Therapeutics. "Akcea is uniquely positioned to maximize the therapeutic and commercial potential of ISIS-APO(a)-L$_{Rx}$. We plan to rapidly advance this new drug to market for patients with high Lp(a) who have no effective treatment options today."

"ISIS-APO(a)-L$_{Rx}$ is greater than 30-fold more potent in humans than the unconjugated drug, ISIS-APO(a)$_{Rx}$. The significant increase in potency and the longer half-life of the drug support the potential for monthly, quarterly or even less frequent dosing. In addition, ISIS-APO(a)-L$_{Rx}$ demonstrates a good tolerability profile. Given these data, we believe that the profile conferred by our LICA technology significantly broadens the patient populations we can target with our LICA drugs by supporting very low volume, infrequent and well tolerated subcutaneous dosing," said Richard Geary, Ph.D., senior vice president of clinical development at Isis Pharmaceuticals. "We look forward to advancing ISIS-APO(a)-L$_{Rx}$ and the seven other LICA drugs we have in our pipeline today and also adding new LICA drugs to our pipeline in the coming years."

ISIS-APO(a)-L$_{Rx}$ is a LICA antisense drug, which is part of Isis' lipid franchise and is being developed and commercialized by Akcea Therapeutics, Isis' wholly owned subsidiary.

ABOUT Lp(a)

Lp(a) is considered a key driver for cardiovascular disease due to its association with an increased risk of coronary heart disease, atherosclerotic plaque formation and calcific aortic valve stenosis. Lp(a) is a lipoprotein particle that is assembled in the liver and consists of the apolipoprotein(a) protein covalently linked to LDL-cholesterol. Lp(a) levels in blood can vary greatly between individuals due primarily to genetic variations in the gene that encodes for apolipoprotein(a). As a result, Lp(a) levels are genetically determined and remain constant throughout the life of the individual. Diet and lifestyle changes have little impact on Lp(a) levels and current therapies are not able to adequately reduce elevated levels of Lp(a) to acceptable levels in patients who have severely elevated Lp(a). As a general guideline for ideal Lp(a) levels, the European Atherosclerosis Society recommends that Lp(a) levels be less than or equal to 50 mg/dL. Additional information is available through Lipoprotein (a) Foundation at www.lipoproteinafoundation.org.

Webcast

At 1:00 p.m. Eastern Time, Nov. 8, 2015, Isis will conduct a webcast to discuss the data presented today for ISIS-APO(a)$_{Rx}$ and ISIS-APO(a)-L$_{Rx}$ and review the overall development plan for the Apo(a) program. A live audio webcast of the presentation will be available on the "Investor & Media" section of the Company's website, www.isispharm.com. Interested parties may listen to the call by dialing 877-443-5662. A replay will be available for a limited time. The slides presented on the webcast will be available on Isis' website at www.isispharm.com at the time of the webcast and for a limited time after.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis is the leading company in RNA-targeted drug discovery and development focused on developing drugs for patients who have the highest unmet medical needs, such as those patients with severe and rare diseases. Using its proprietary antisense technology, Isis has created a large pipeline of first-in-class or best-in-class drugs, with over a dozen drugs in mid- to late-stage development. Drugs currently in Phase 3 development include volanesorsen, a drug Isis is developing and plans to commercialize through its wholly owned subsidiary, Akcea Therapeutics, to treat patients with familial chylomicronemia syndrome and familial partial lipodystrophy; ISIS-TTR$_{Rx}$, a drug Isis is developing with GSK to treat patients with all forms of TTR amyloidosis; and ISIS-SMN$_{Rx}$, a drug Isis is developing with Biogen to treat infants and children with spinal muscular atrophy. Isis' patents provide strong and extensive protection for its drugs and technology. Additional information about Isis is available at www.isispharm.com.

ABOUT AKCEA THERAPEUTICS

Akcea Therapeutics is a development and commercialization company focused on transforming the lives of patients with serious cardiometabolic lipid disorders. Established as a wholly-owned subsidiary of Isis Pharmaceuticals, Inc., Akcea has a robust portfolio of development-stage drugs covering multiple targets and disease states using advanced RNA-targeted antisense therapeutics. Akcea's drug pipeline includes novel antisense drugs designed to address a number of lipid risk factors, including LDL-Cholesterol, apoC-III, triglycerides and Lp(a). Akcea's most advanced program, volanesorsen, is in Phase 3 development to treat patients with ultra-orphan lipid disorders that are characterized by extremely high triglycerides and ApoC-III, including familial chylomicronemia syndrome (FCS) and familial partial lipodystrophy (FPL). Akcea is located in Cambridge, Massachusetts. Additional information about Akcea is available at www.akceatx.com.

ISIS PHARMACEUTICALS' FORWARD-LOOKING STATEMENT

This press release includes forward-looking statements regarding Isis' business, the business of Akcea Therapeutics, the therapeutic and commercial potential of Isis' LICA technology, the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-APO(a)$_{Rx}$ and ISIS-APO(a)-L$_{Rx}$ for the treatment of lipid disorders. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2014, and its most recent quarterly report on Form 10-Q, which are on file with the SEC. Copies of these and other documents are available from the Company.

In this press release, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

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